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REACTION SCHEME 2

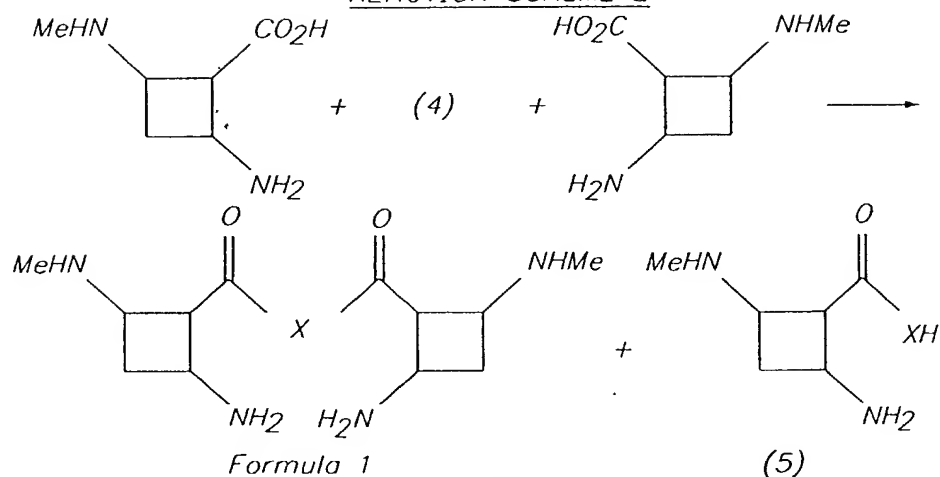


FIG. 1

REACTION SCHEME 3

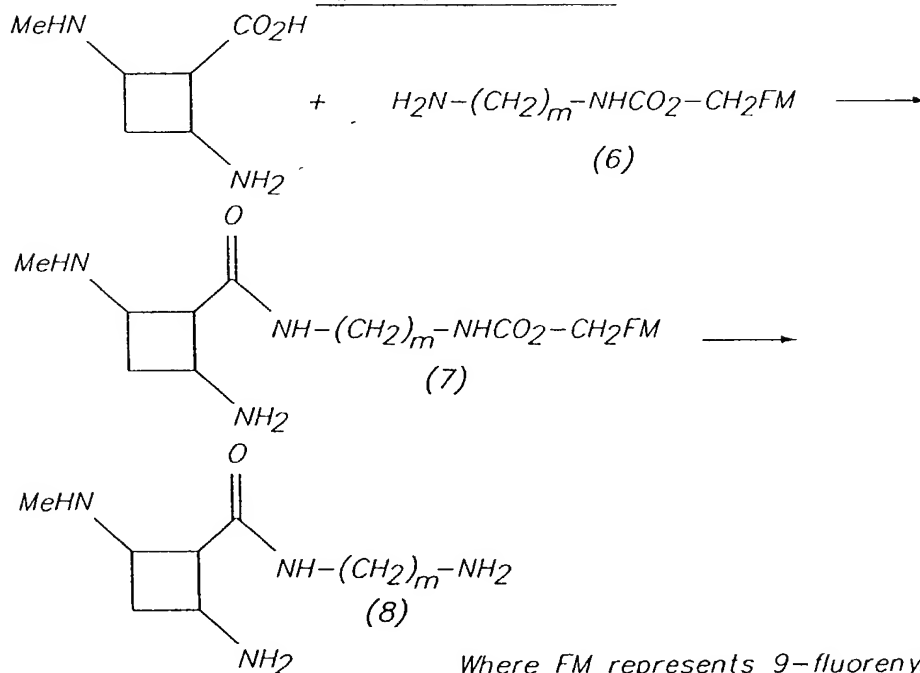
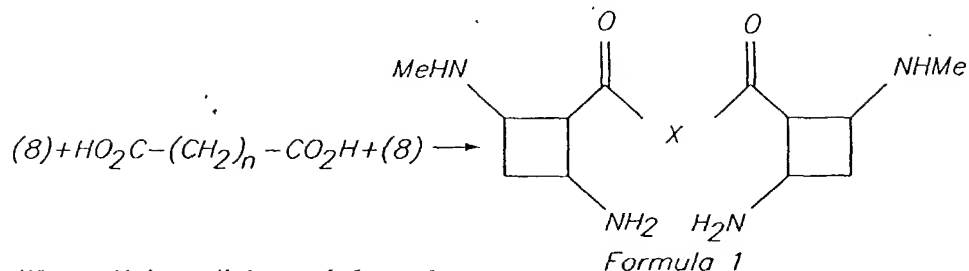


FIG. 2

Where FM represents 9-fluorenyl.,
and m is an integer of 1-20

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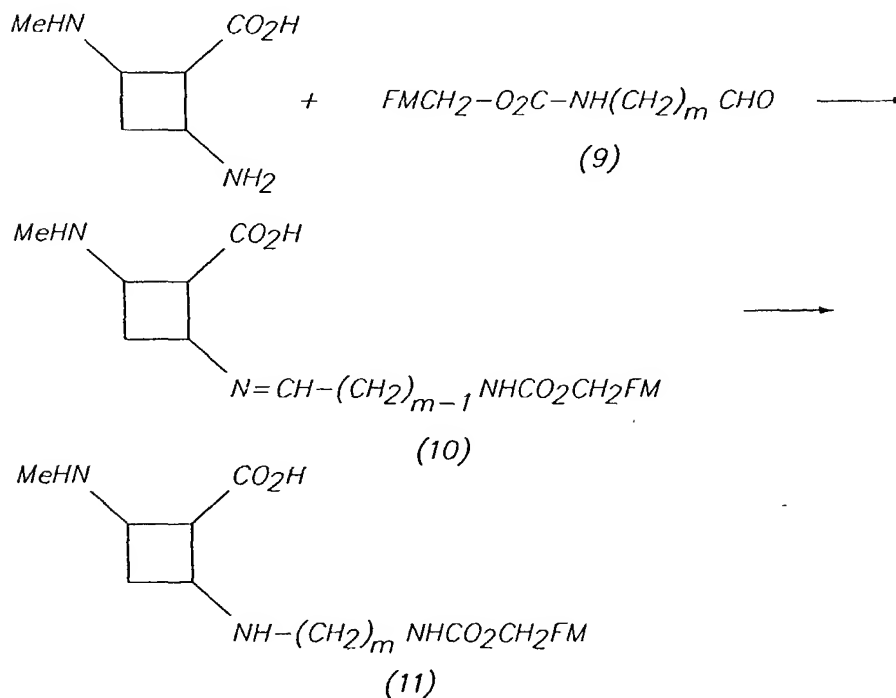
REACTION SCHEME 4



Where X is a linker of formula:
 $-\text{NH}-(\text{CH}_2)_m-\text{NHC(O)}(\text{CH}_2)_n\text{C(O)}\text{NH}(\text{CH}_2)_m-\text{NH}-$
 in which m and n are independently integers of 1-20

FIG. 3

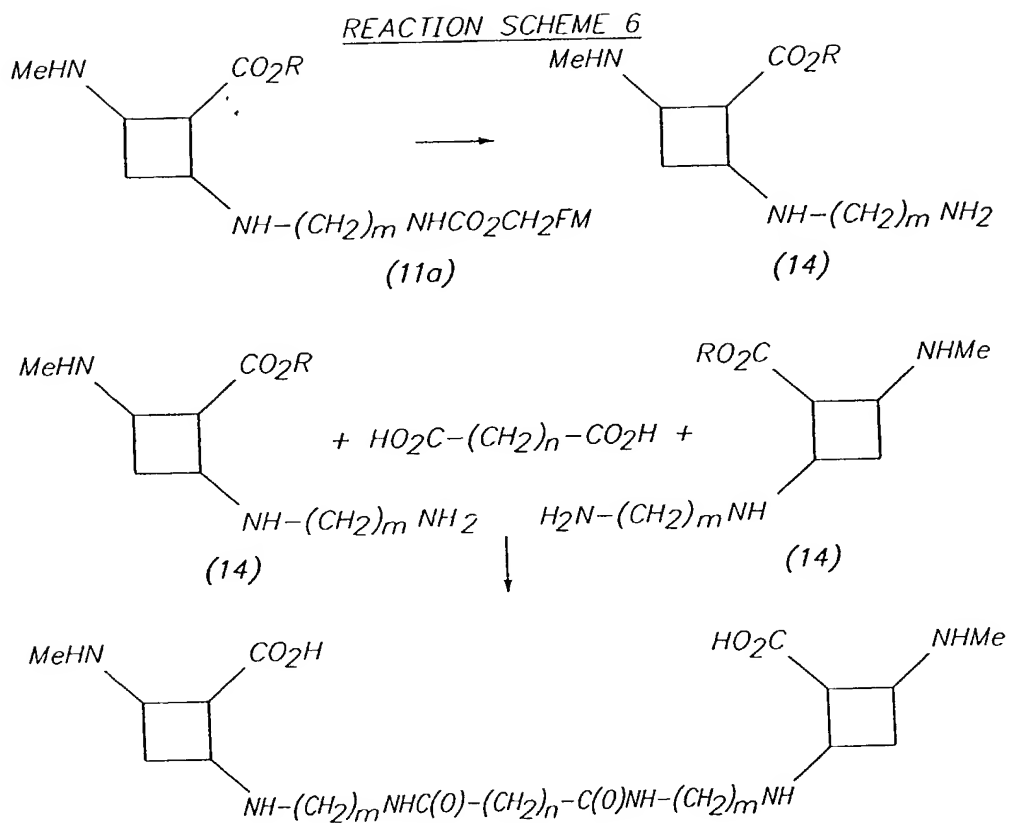
REACTION SCHEME 5



in which m is an integer of 1-20, and FM is 9-fluorenyl

FIG. 4

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where R is a protecting group, such as an ester, m and n are as defined above, and FM is 9-fluorenyl

FIG. 5

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REACTION SCHEME 7

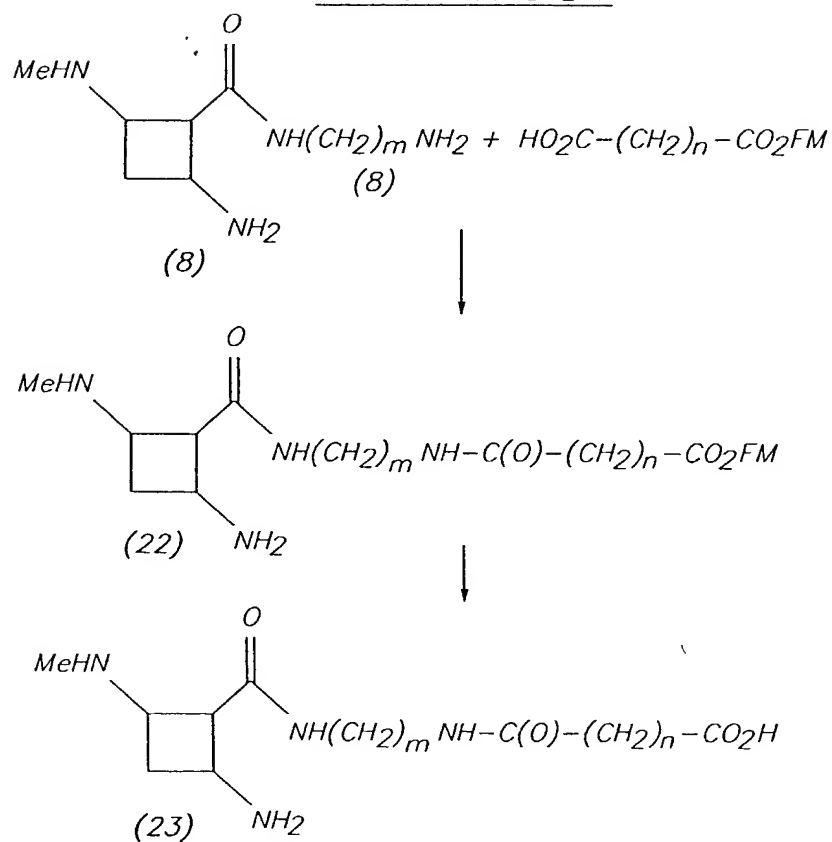
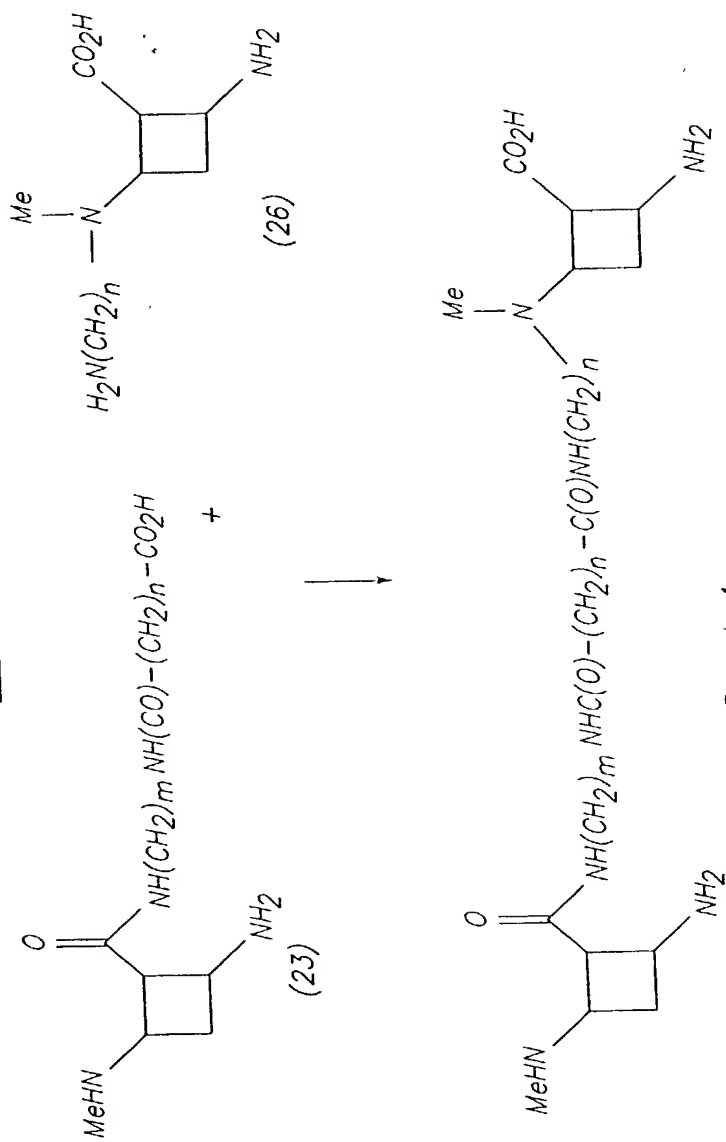


FIG. 6

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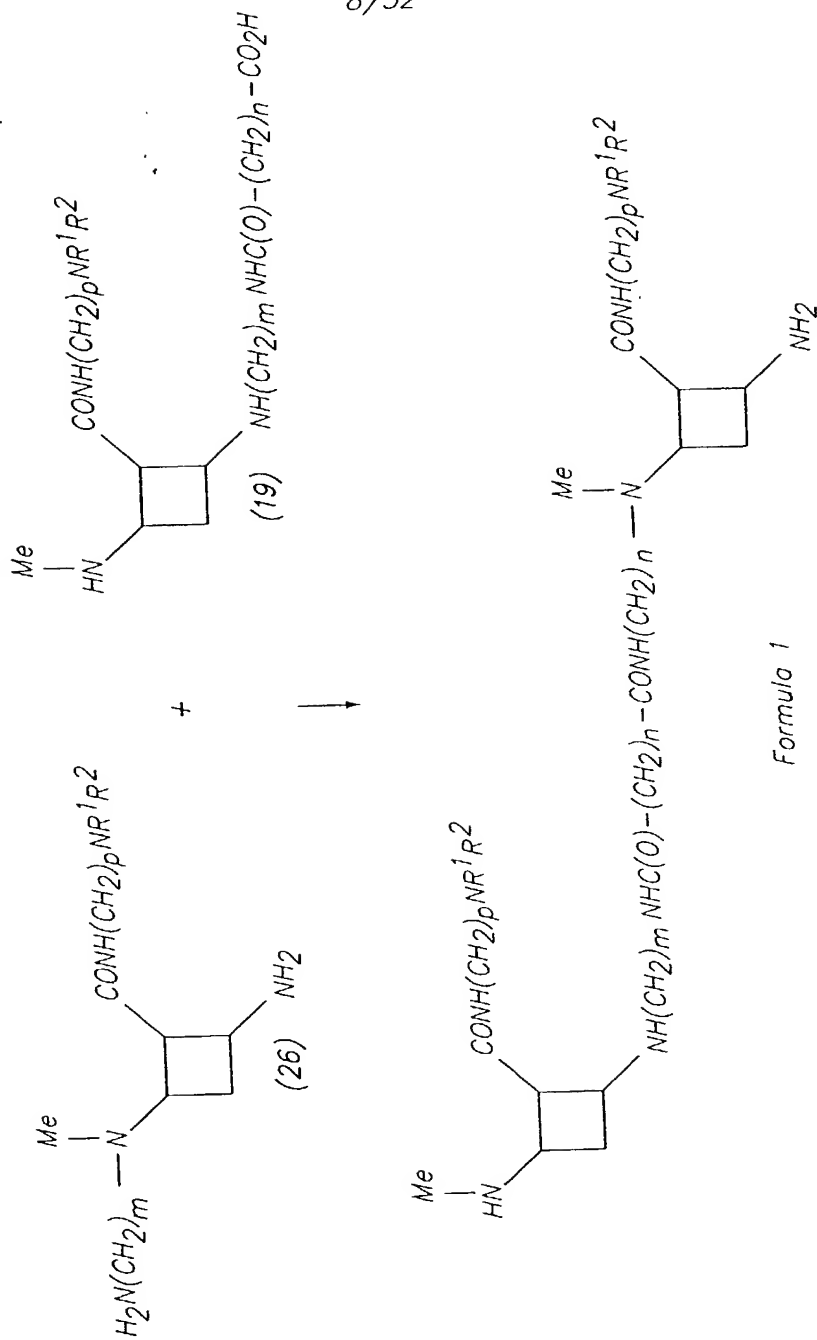
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REACTION SCHEME 10

Formula 1

FIG. 9

REACTION SCHEME 11



Formula 1

FIG. 10

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FIG. 12

Examples of dimeric display

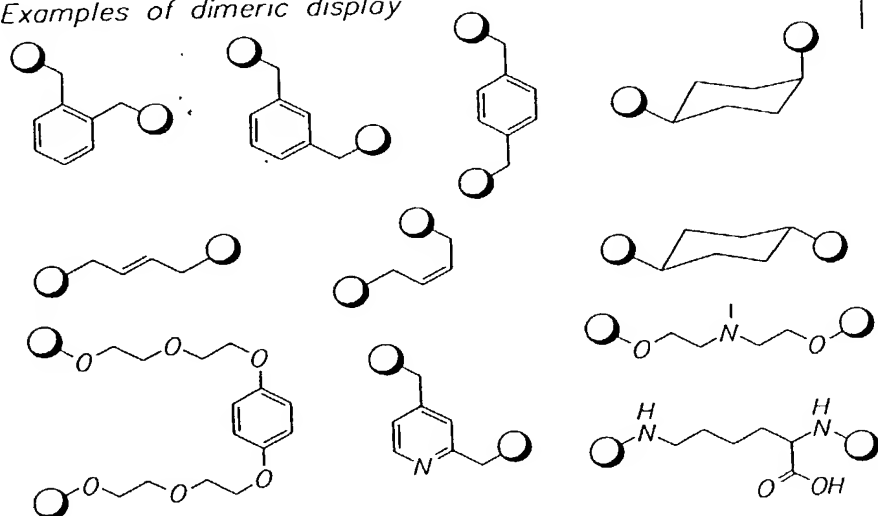
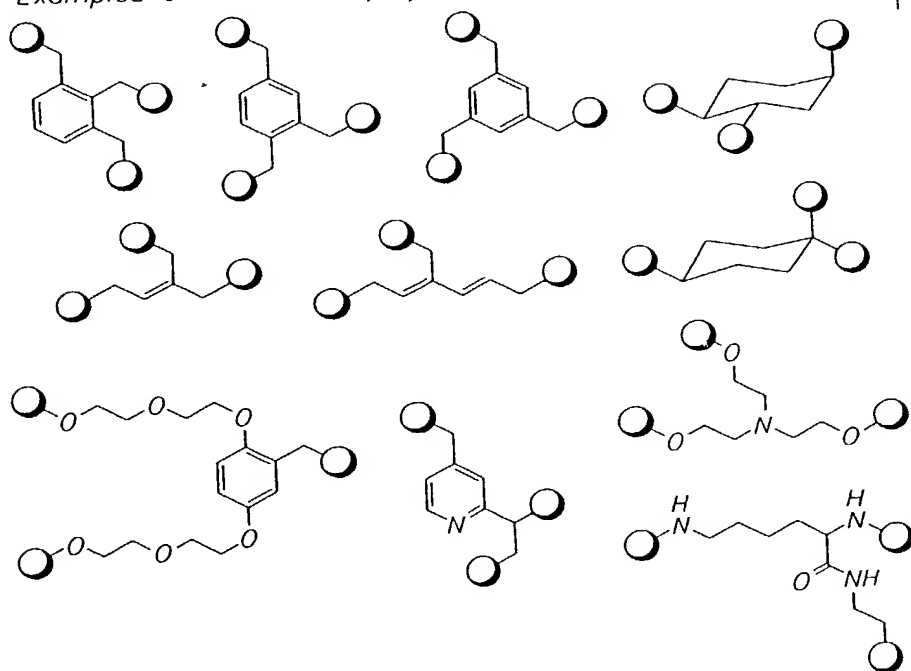
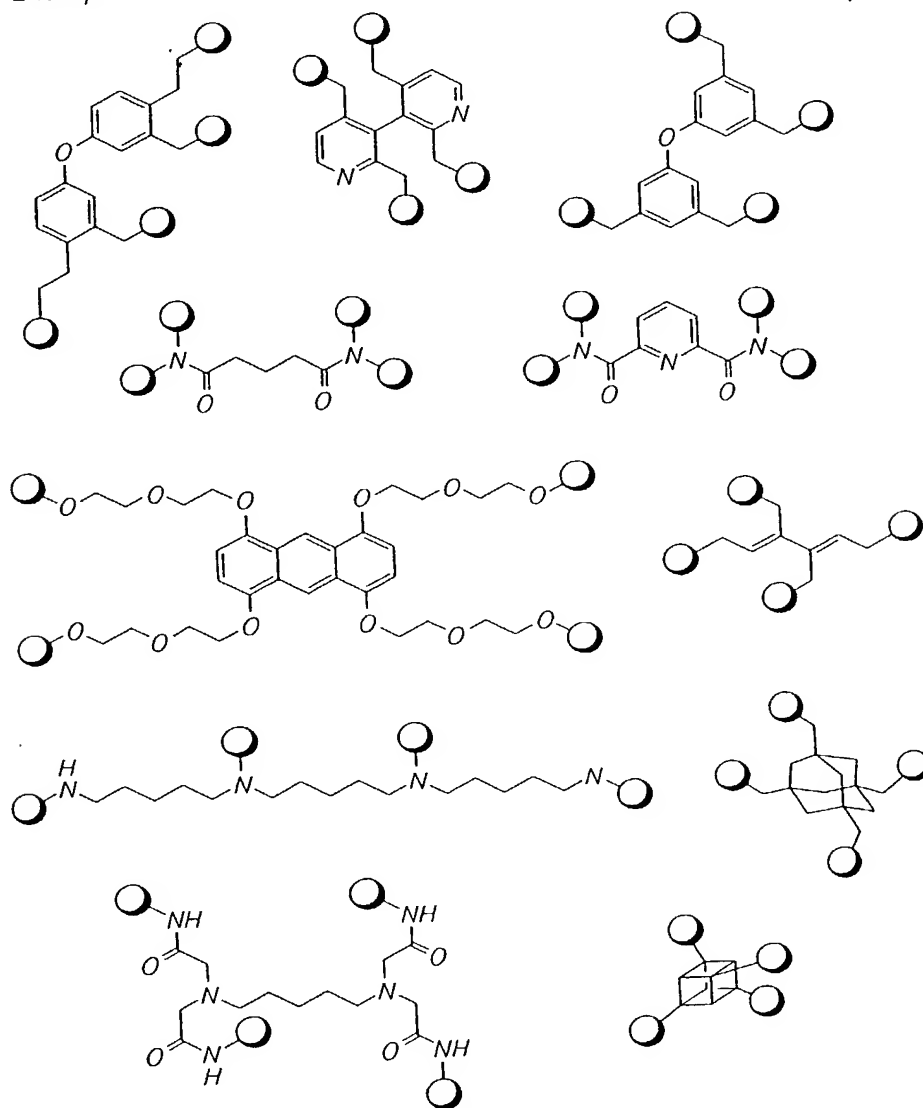


FIG. 13

Examples of trimeric display



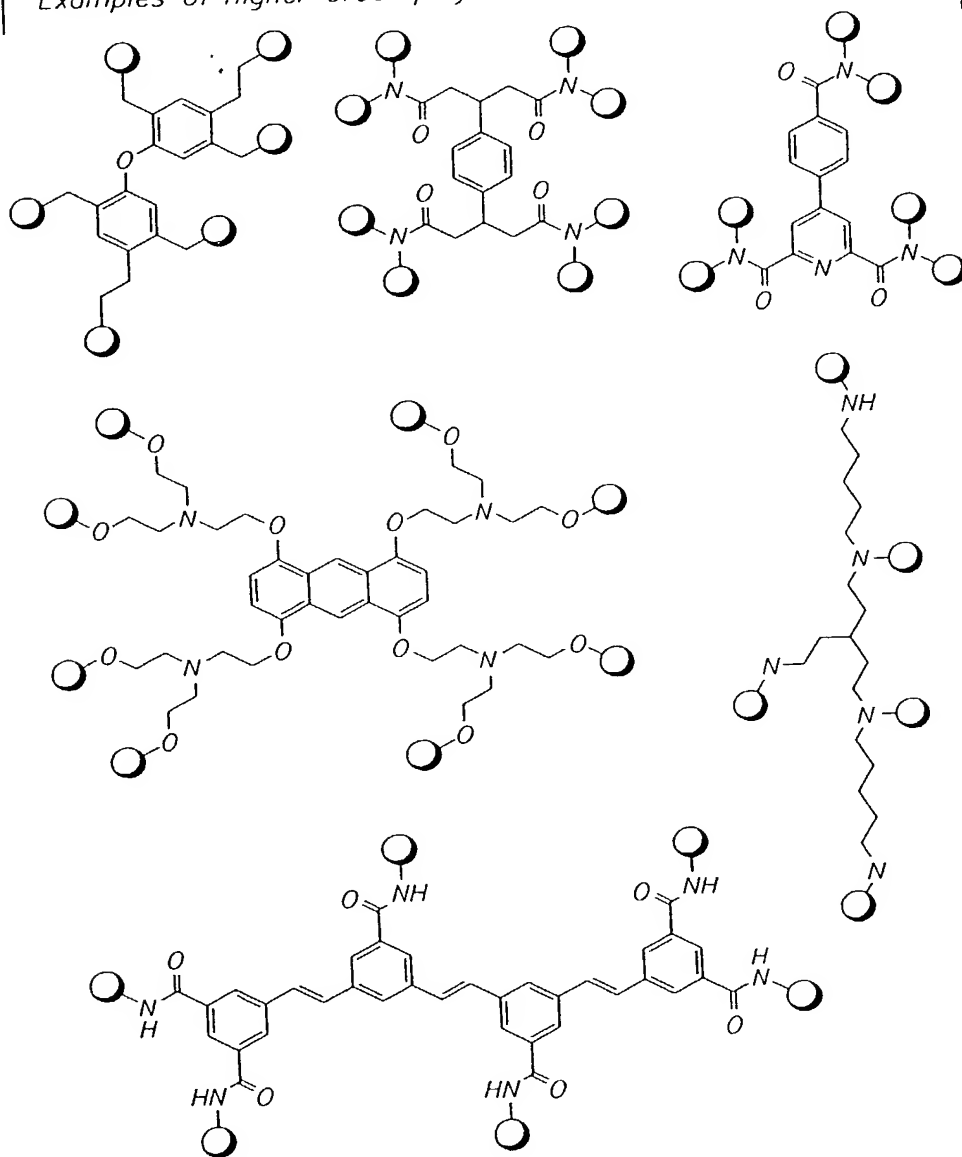
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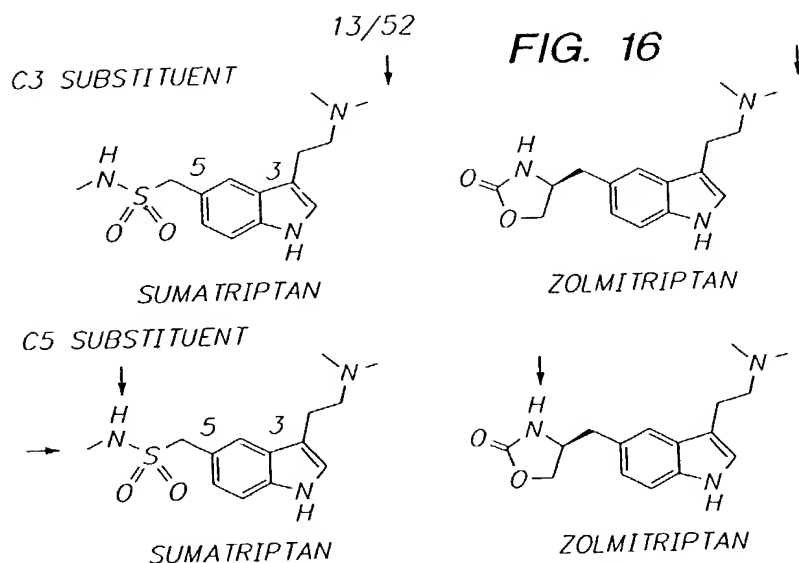
FIG. 14*Examples of tetrameric display*

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FIG. 15

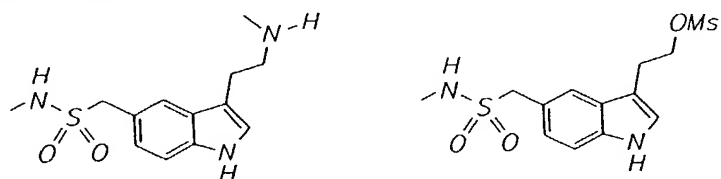
Examples of higher order polyvalent display



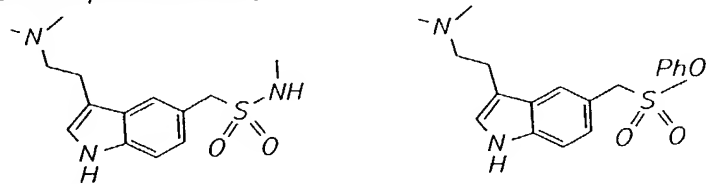
**FIG. 17**

SUMATRIPTAN BUILDING BLOCKS

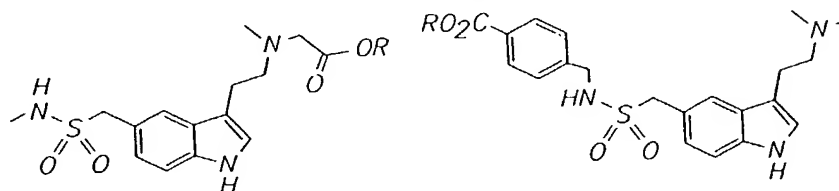
C3PharmacophoricBuilding Blocks



C5PharmacophoricBuilding Blocks



Pharmacophoric Building Blocks that contain a Spacer

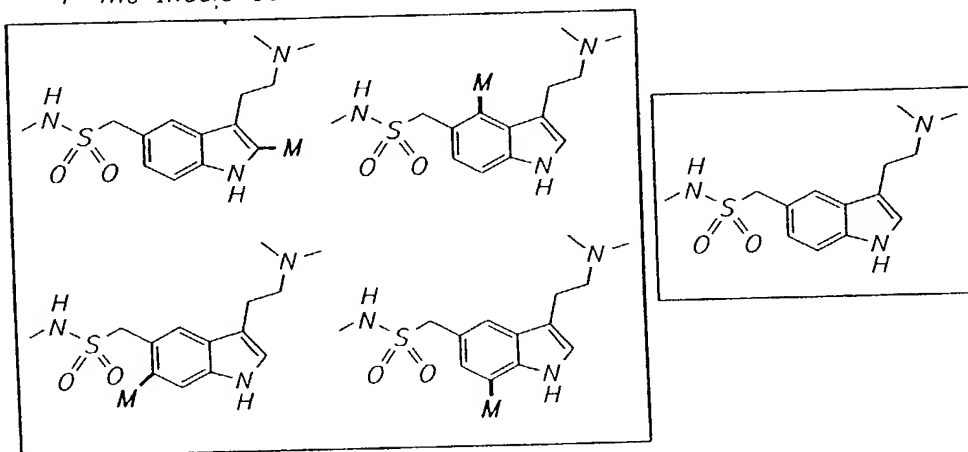


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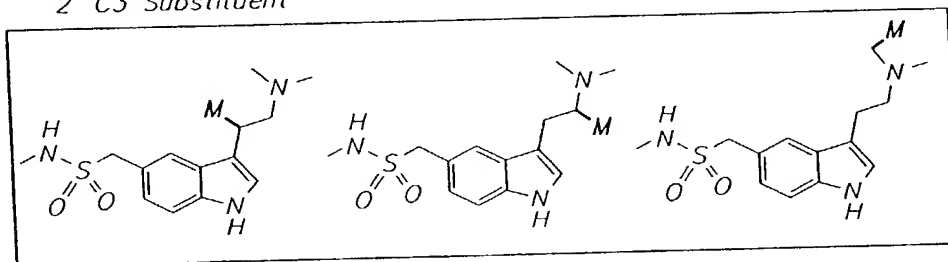
FIG. 18

MULTIVALOMERS OF SUMATRIPTAN

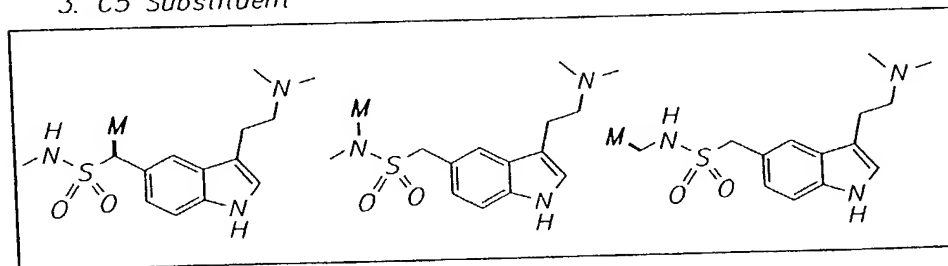
1 The Indole Core



2 C3 Substituent

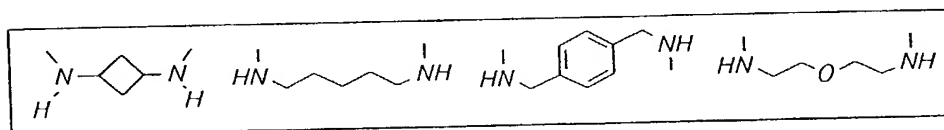
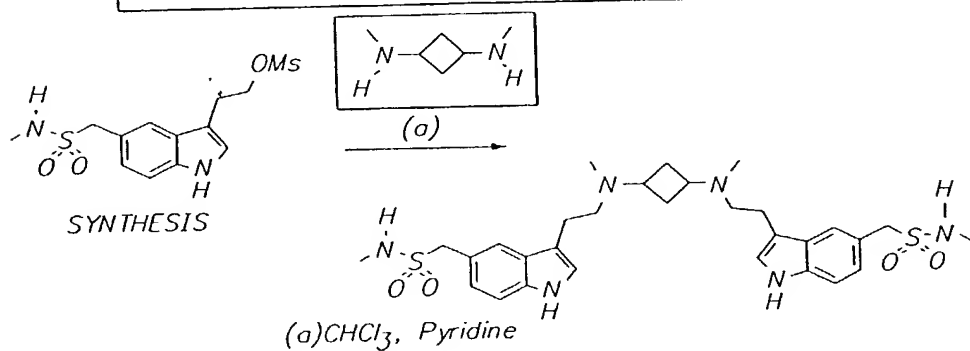


3. C5 Substituent

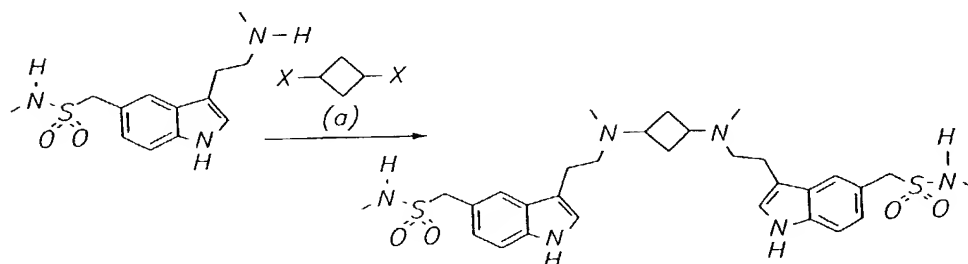


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C3 ELECTROPHILE TO PROVIDE MULTIVALOMERS



C3 NUCLEOPHILE TO PROVIDE MULTIVALOMERS


$$X = -CH_2Br \quad (o)DCM, \text{ pyrdine}$$
$$X = -CHO \quad (a) DCM, NaBH(OAc)_3, AcOH$$

$X = -CO_2H$ (a) DIC, DIPEA, DMF

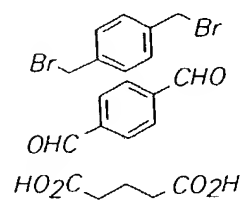
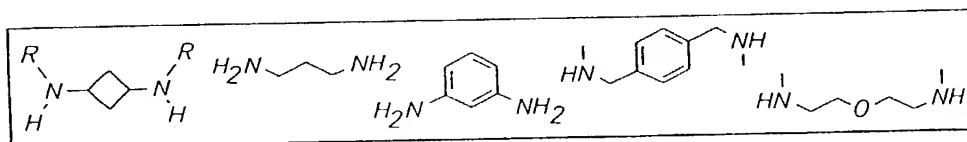
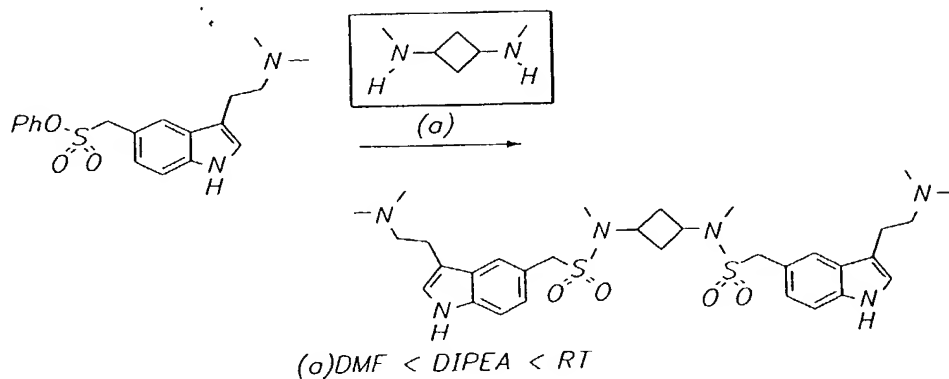


FIG. 19

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C5 FUNCTIONALIZATION OF SUMATRIPTAN

Electrophilic Pharmacophoric Monovalomer



Nucleophilic Pharmacophoric Monovalomer

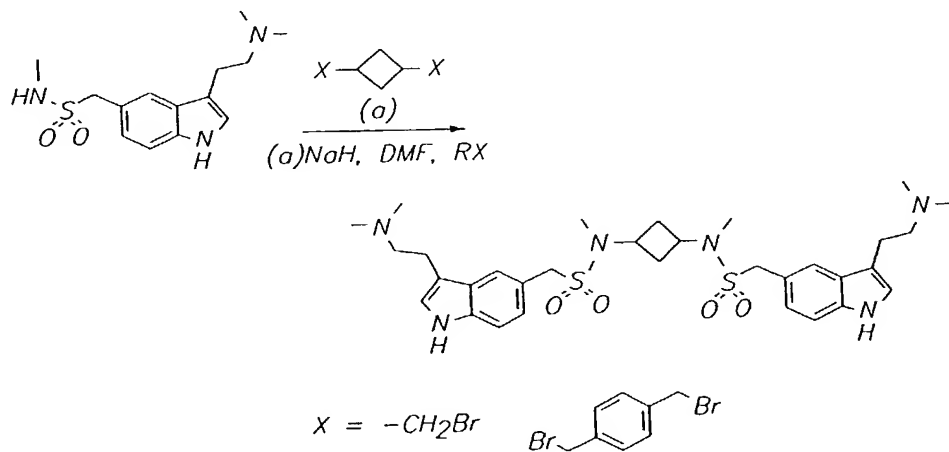
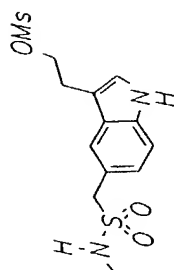
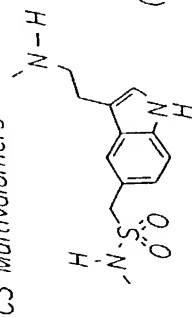


FIG. 20

SUMATRIPTAN SPECIFICS

C3 Multivalomers



C5 Multivalomers

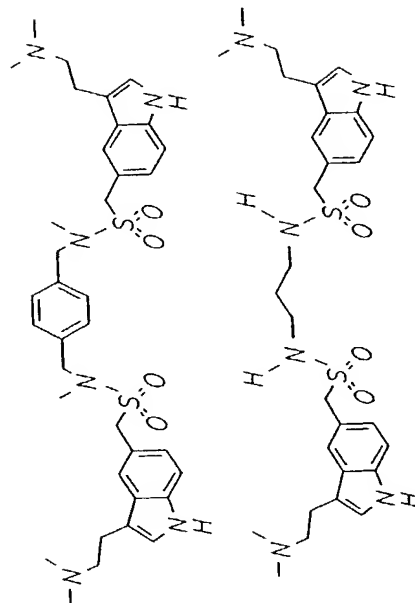
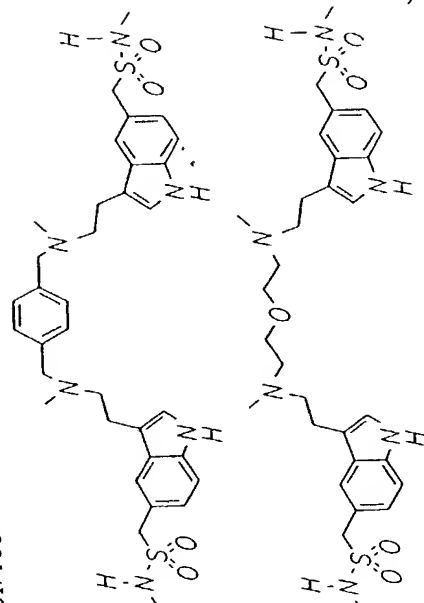
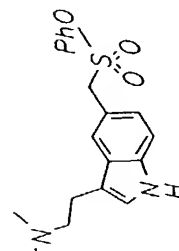
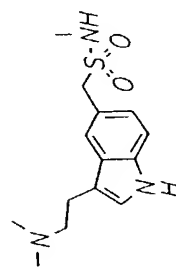


FIG. 21

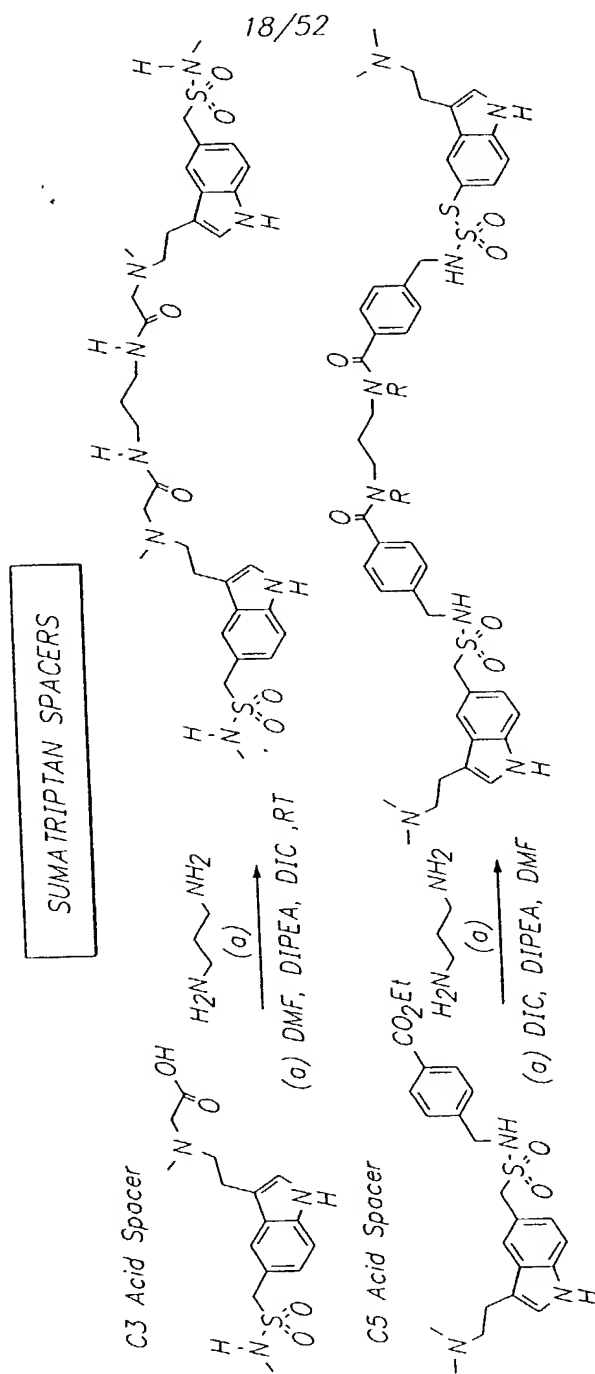
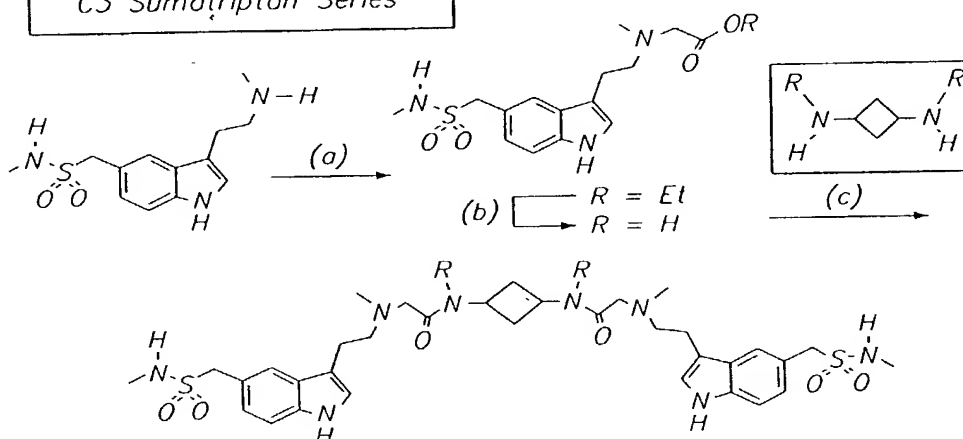


FIG. 22

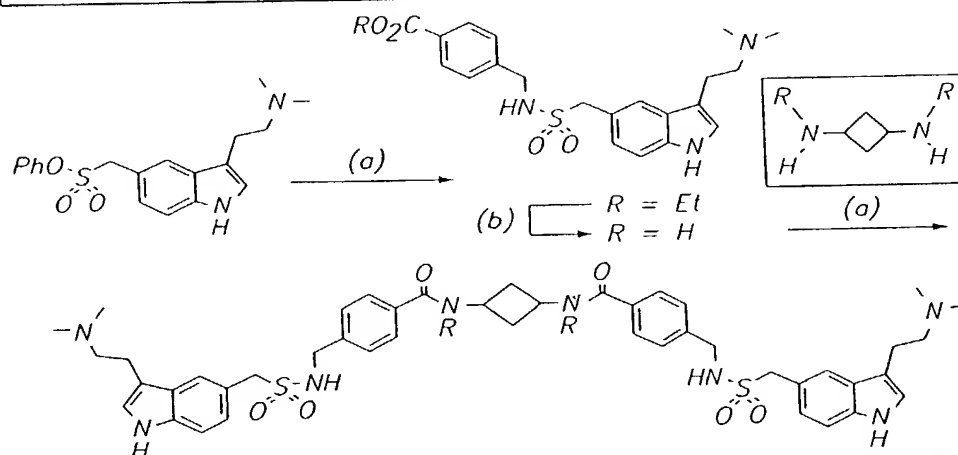
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Introduction of Spacer To Facilitate Multivalomer Formation

C3 Sumatriptan Series



C5 Sumatriptan Series



(a) DIPEA, DCM, $\text{BrCH}_2\text{CO}_2\text{Et}$ (b) LiOH , THF, H_2O , (c) DIC, DIPEA, DMF

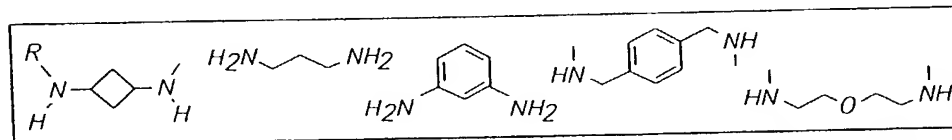
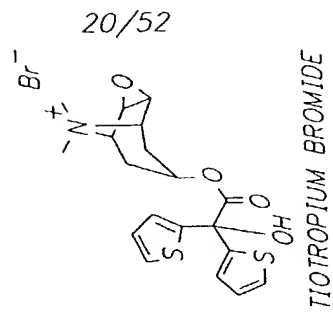
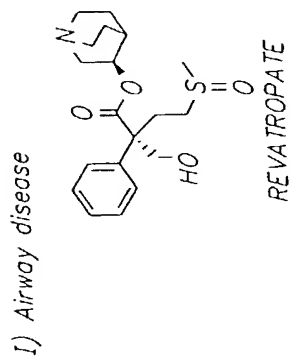
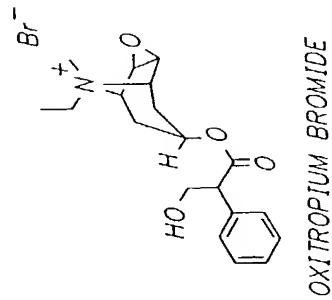
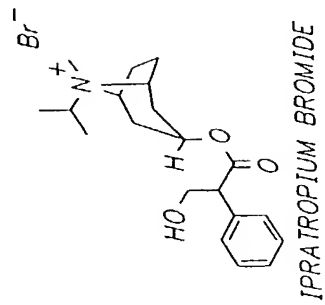


FIG. 23

MUSCARINIC ANTAGONISTS USED IN AIRWAY DISEASE

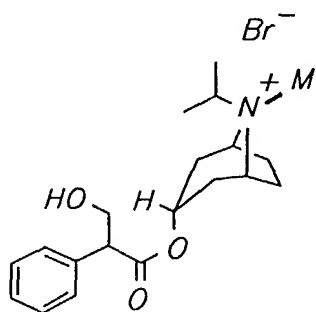


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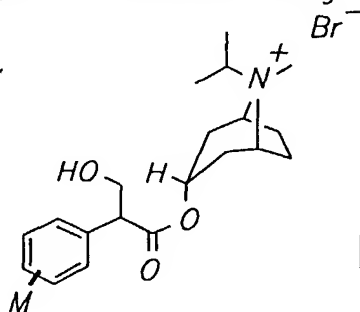
FIG. 24

SITES FOR DIMERIZATION

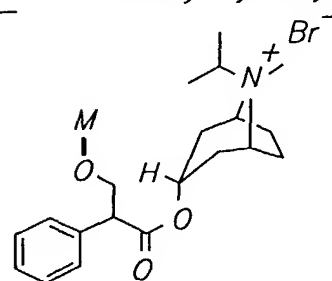
Nitrogen Atom of Tropane Core



Aromatic Ring

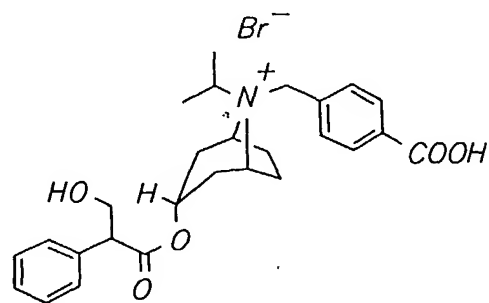
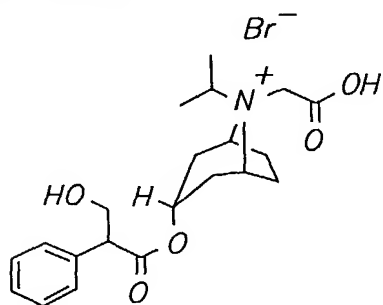


Primary Hydroxyl



Suitable, Pharmacophoric Building Blocks

*Nitrogen Atom of Tropane Core
Acid Series*



Amine Series

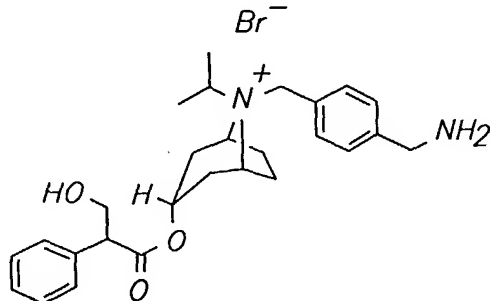
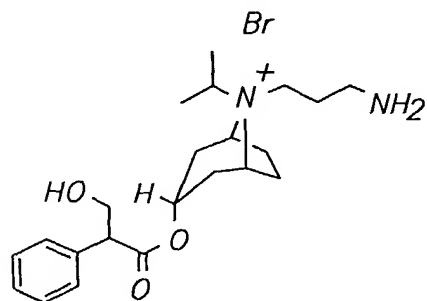
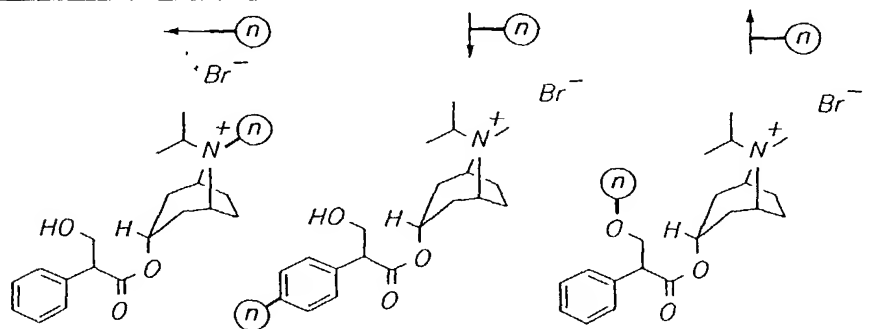


FIG. 25

Ipratropium Multivalomers 1- Different points of Attachment



n defines the valency of the multivomer
 ○ defines the framework core
 → distinguishes the differing points of attachment of ipratropium

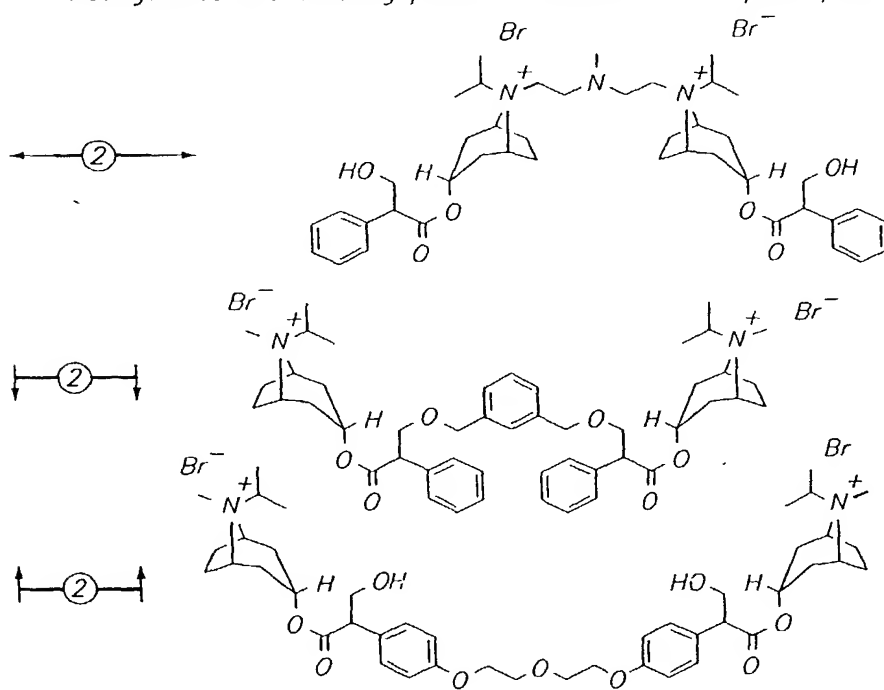


FIG. 26

Ipratropium Multivalomers 2-Alternative Framework Cores

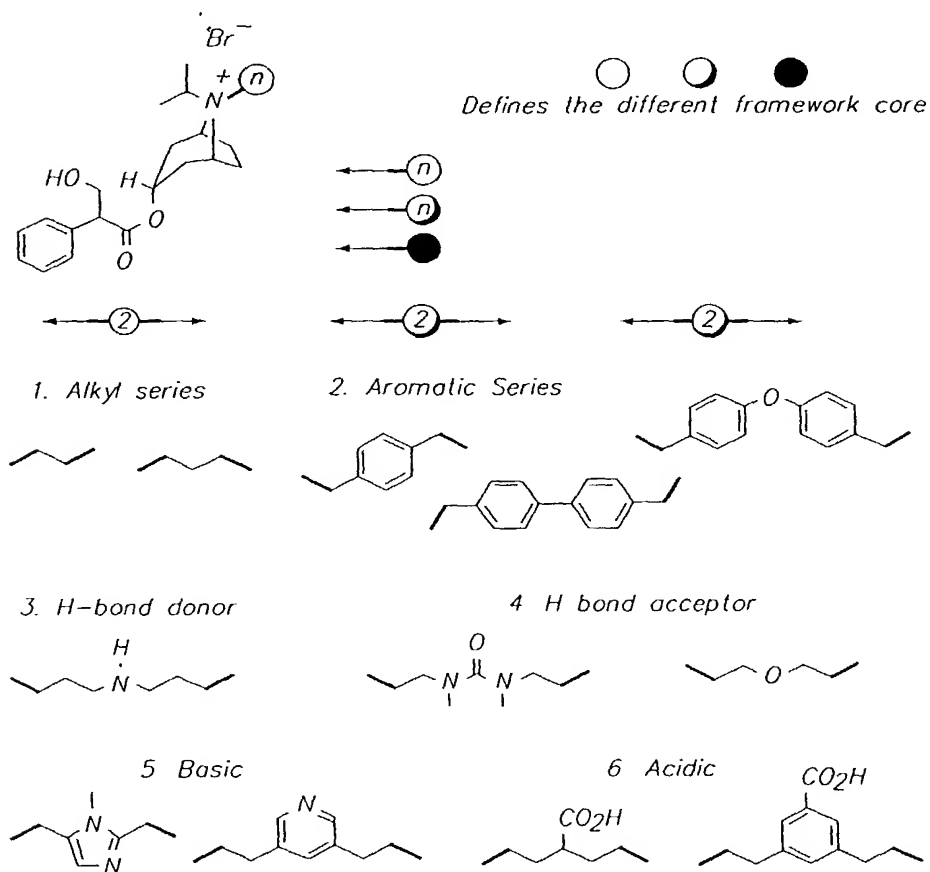


FIG. 27

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Ipratropium Multivalomers 3-Alternative Framework Valency

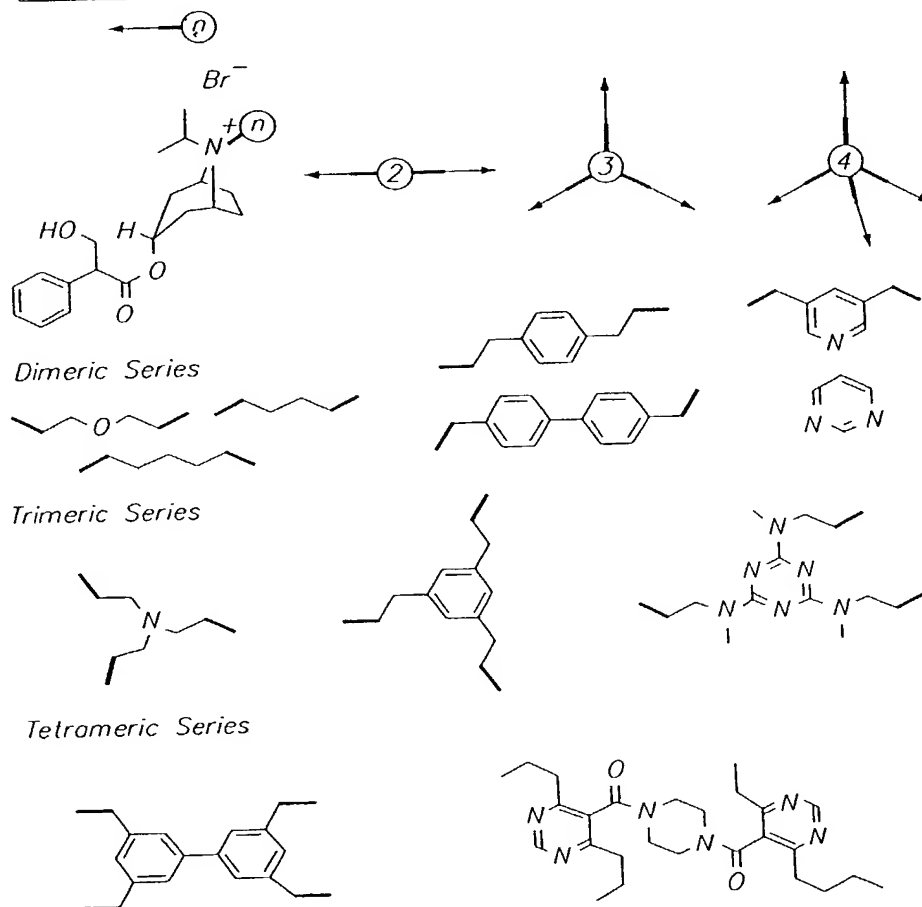


FIG. 28

Ipratropium Multivalomers 4-Relative Pharmacophore Orientation

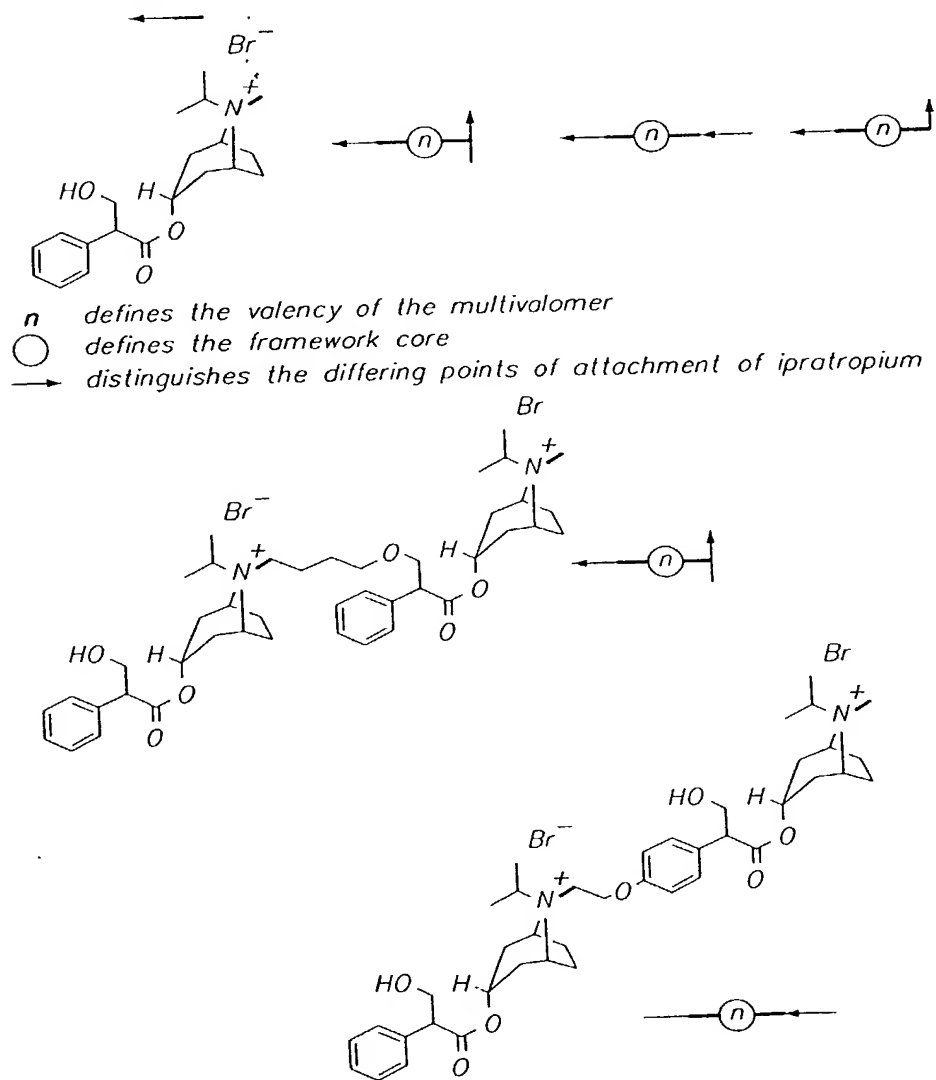


FIG. 29

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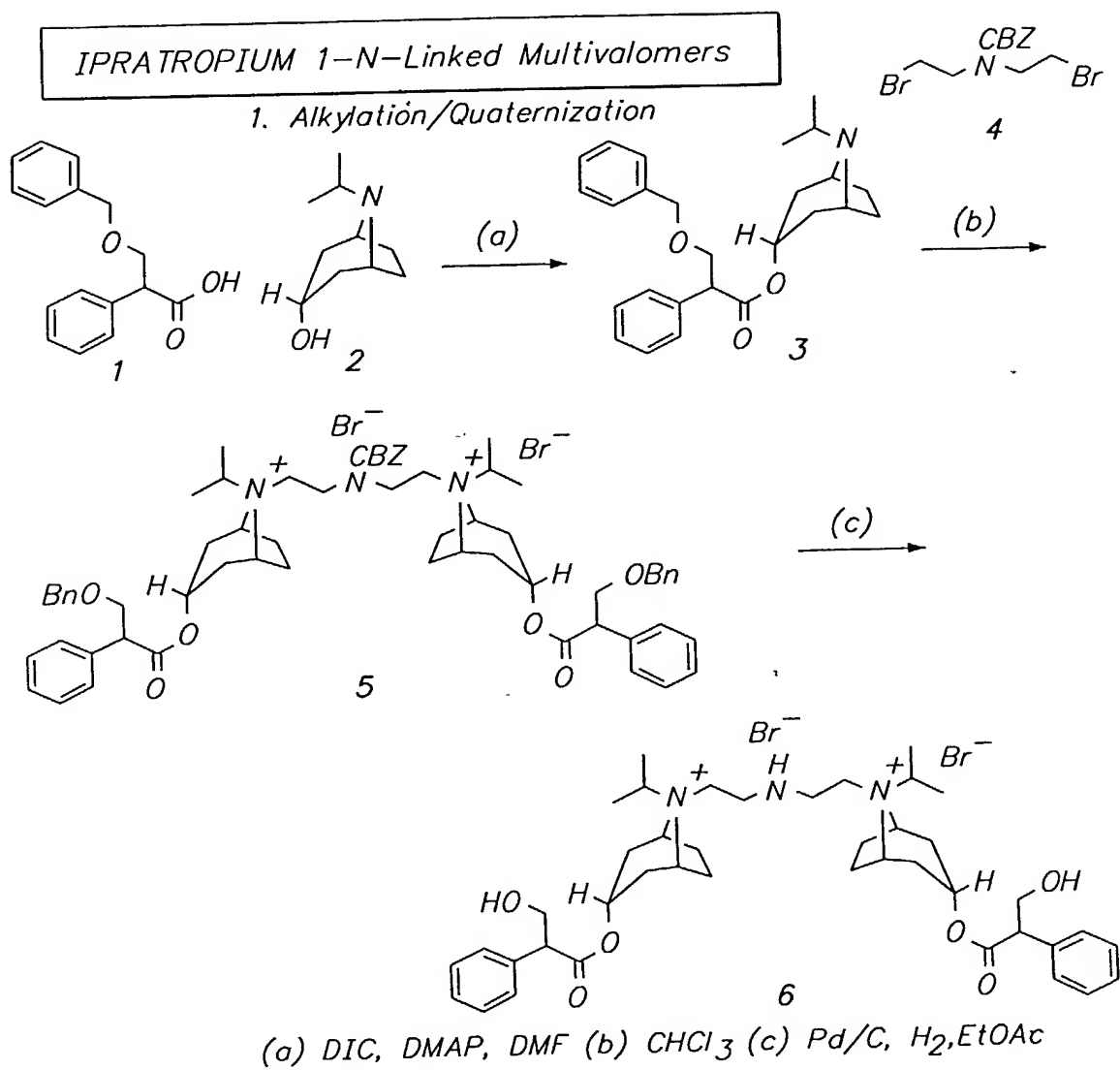
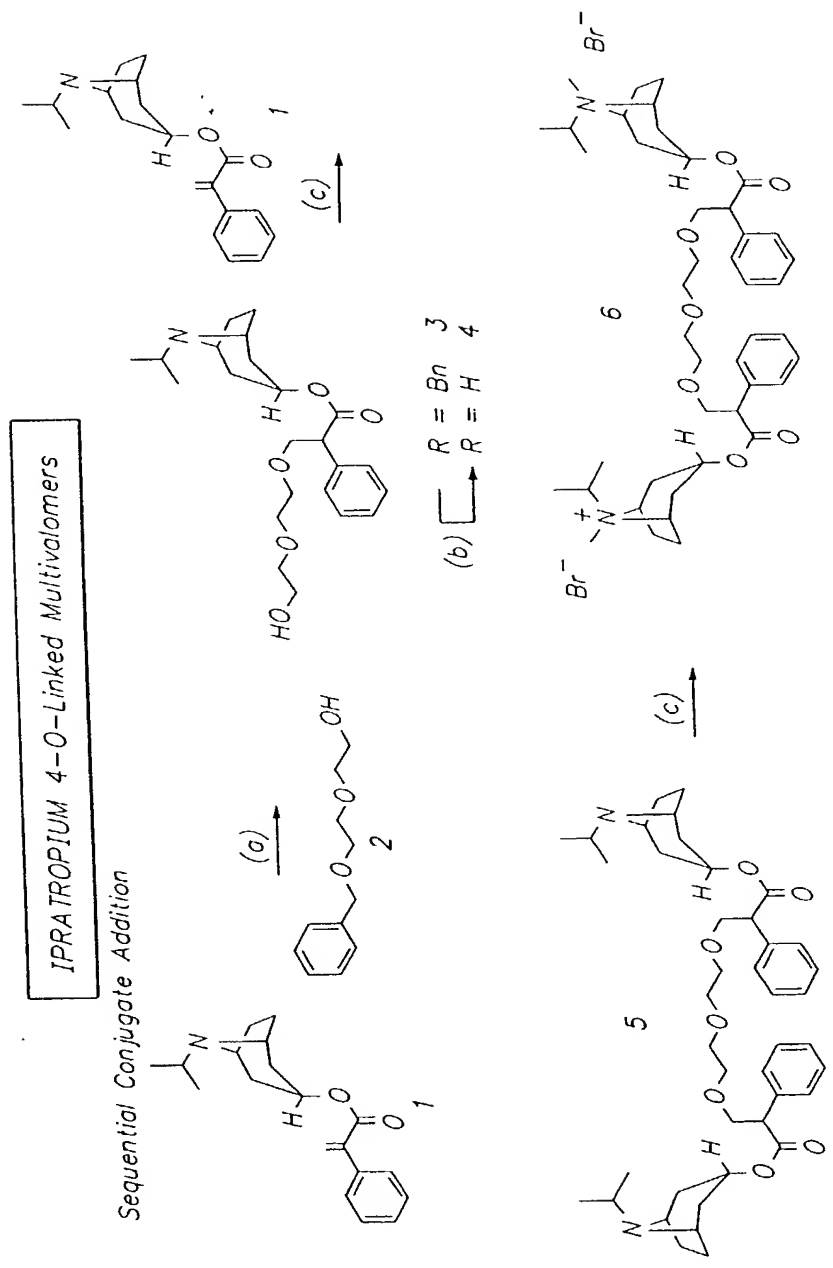


FIG. 30

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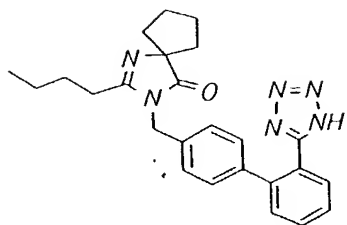
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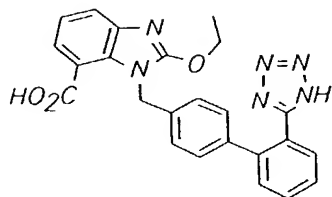
(a) NaH, DME, heat (b) Pd/C, H₂, EtOAc (c) NaH, DME, heat (d) MeBr, CHCl₃, heat

FIG. 33

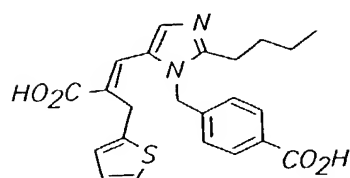
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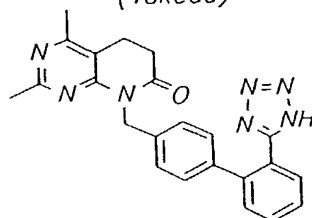
IRBESARTAN
(Sanofi)



CANDESARTAN (Atacand)
(Takeda)

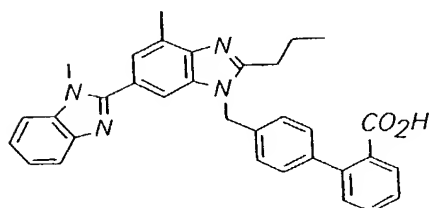


EPROSARTAN (Tevetan)
(Smith KlineBeecham)

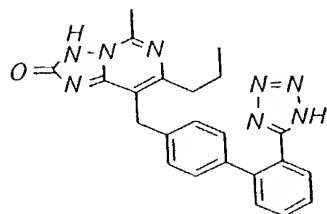


TASOSARTAN (Verdia)
(Wyeth-Ayerst)

FIG. 35



TELMISARTAN
(Boehringer Ingelheim)
Phase III



RIPISARTAN
(Bristol Myers Squibb)
Phase II

Phase II
CS-866 Sankyo
DA-727 Daiichi
KRH-594 Wakunaga
LR-B/081 Lusofarmaco
TAK-536 Takeda
YM-358 Yamanouchi

FIG. 36

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Lorsartan Multivalomers 2-Differing Valency of Multivalomer

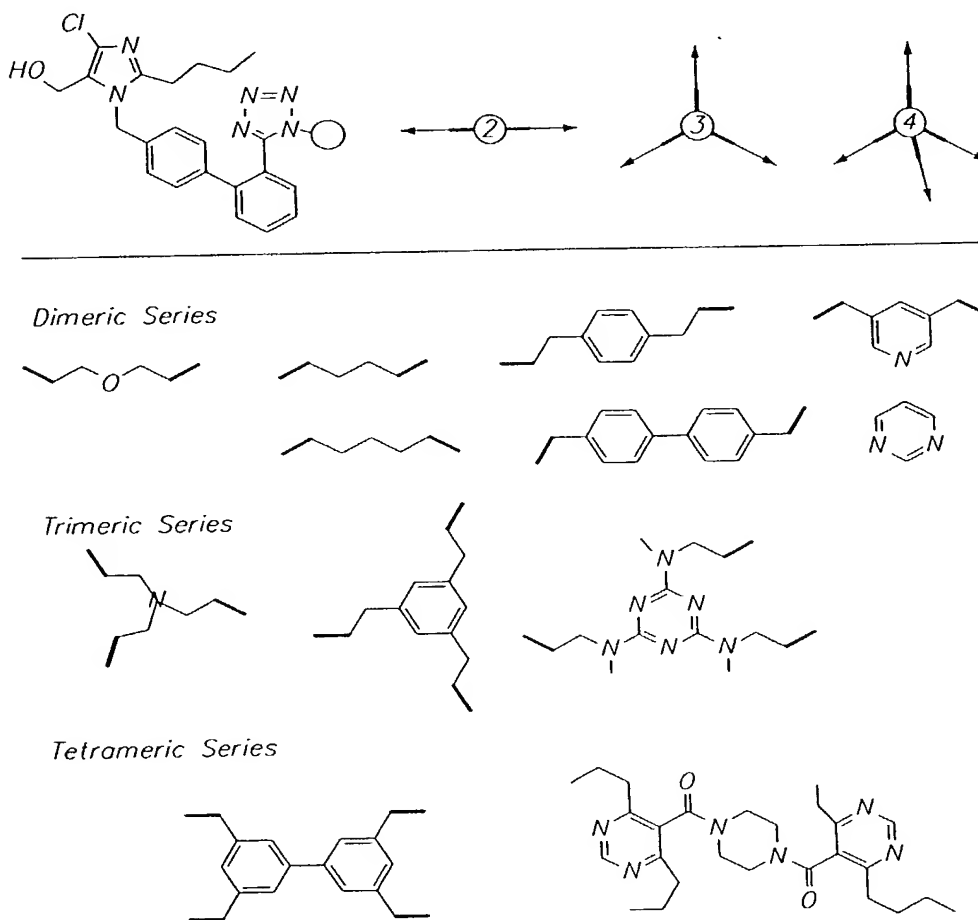
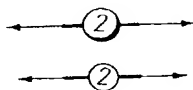
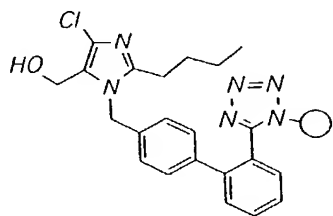


FIG. 40

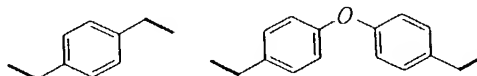
Lorsartan Multivalomers 3-Differing Framework Building Blocks



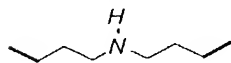
1. Alkyl Series



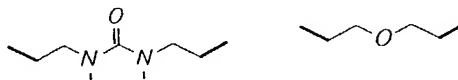
2. Aromatic Series



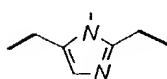
3 H-bond donor



4 H bond acceptor



5 Basic



6 Acidic

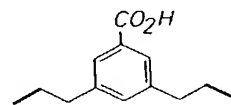
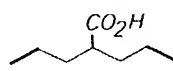
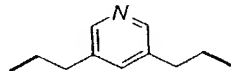


FIG. 41

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Losartan Multivalomers 5-Heterovalomers

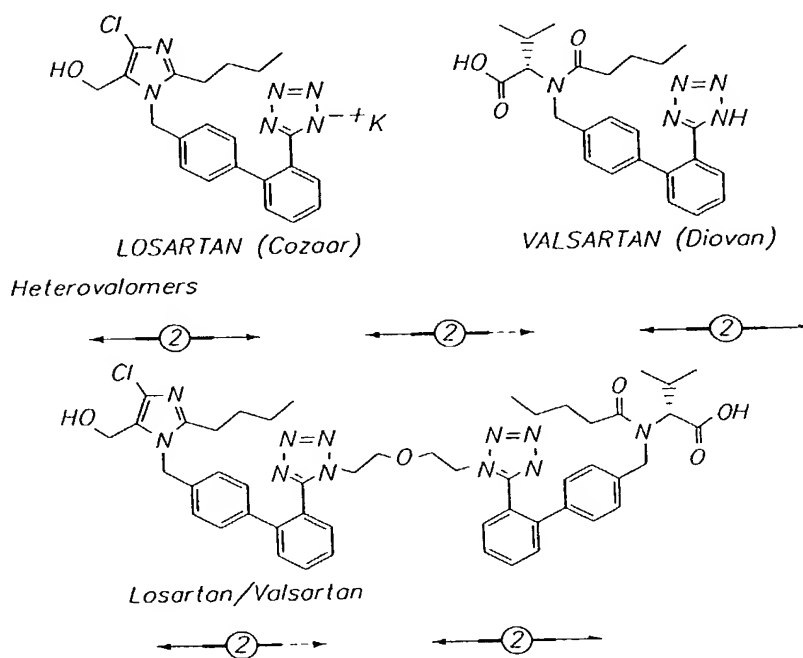


FIG. 43

Losartan Multivalomers Synthesis 1-Hydroxyl Linked Multivalomer

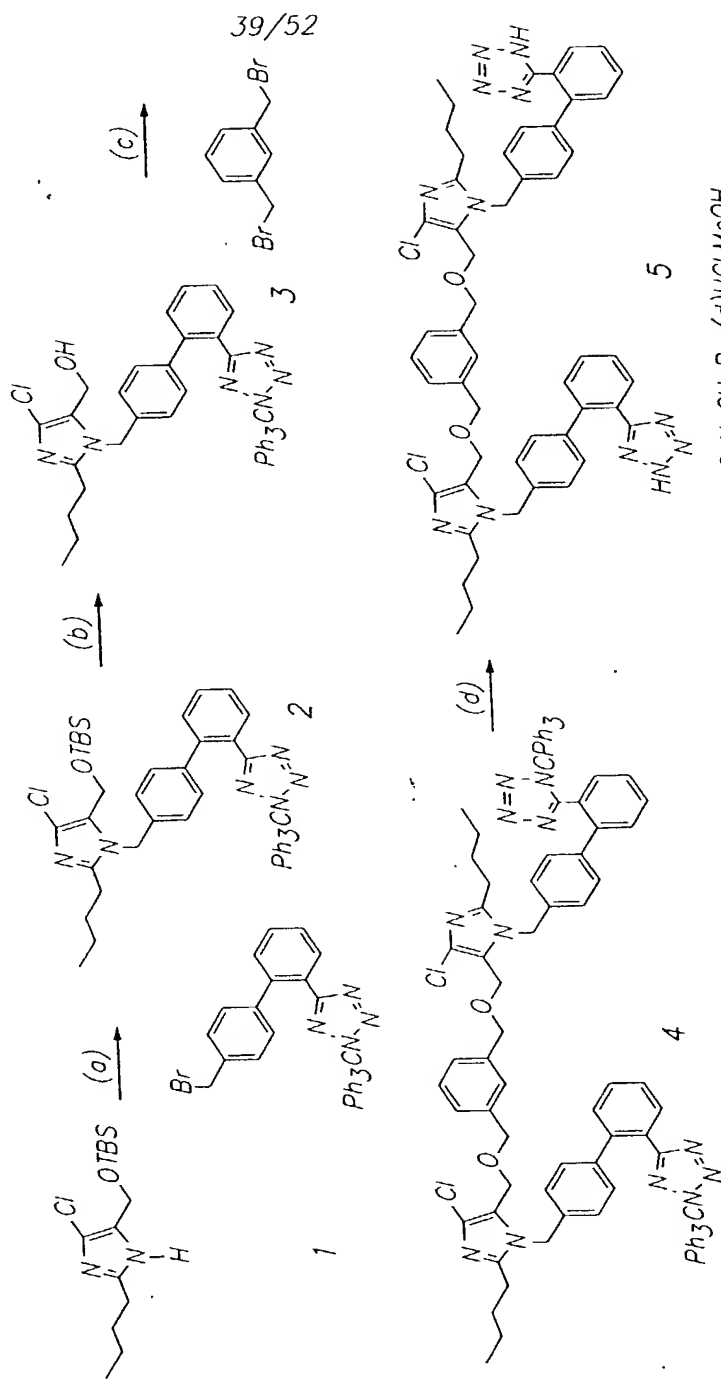


FIG. 44

Losartan Multivalomer Synthesis 2-Hydroxyl Linked Multivalomer

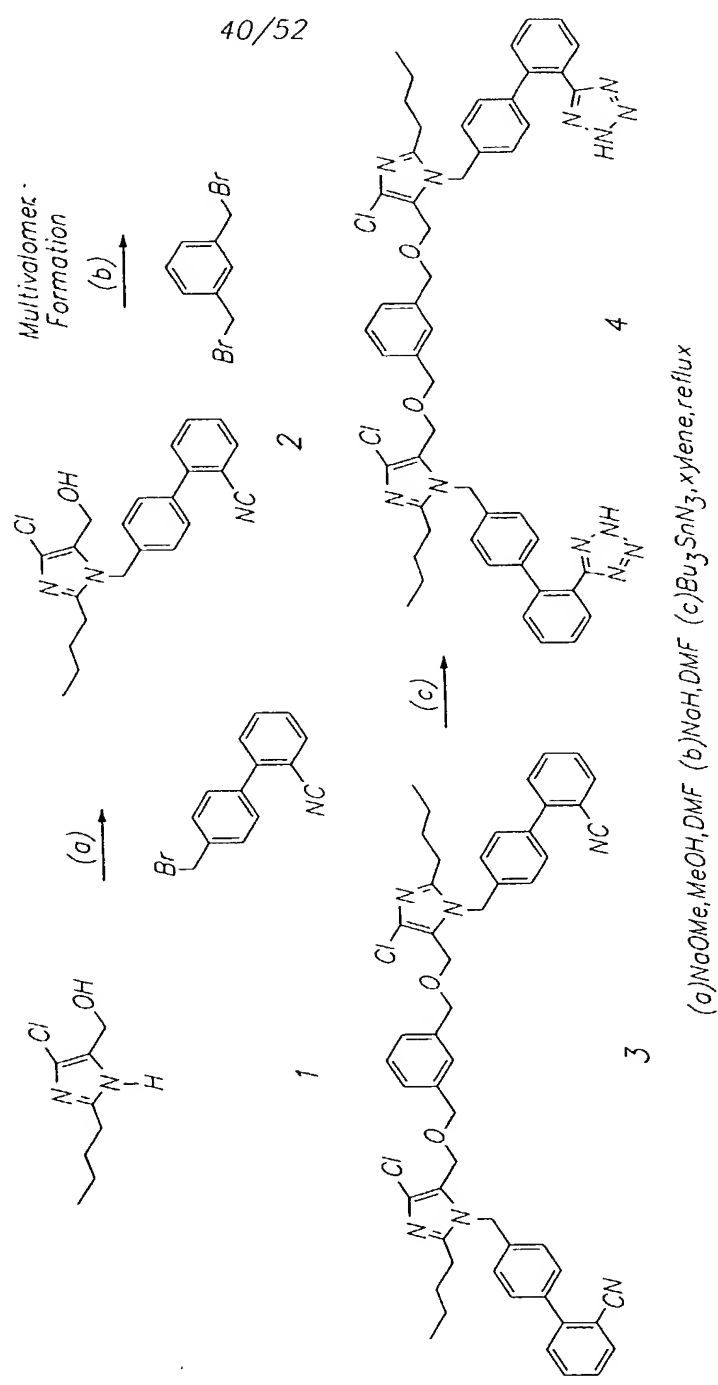


FIG. 45

[illegible]

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Multivalomer Formation

(a)

(b)

1

2

3

The diagram illustrates the multivalomer formation of a triazine-based polymer. It shows three chemical structures labeled 1, 2, and 3. Structure 1 is a triazine monomer with a central triazine ring. One nitrogen is substituted with a 4-cyanophenyl group, another with a 4-(4-bromophenyl)phenyl group, and the third with a 4-(4-chlorophenyl)phenyl group. Arrows labeled (a) and (b) point from structure 1 to structures 2 and 3, respectively. Structure 2 is a linear polymer with a central triazine ring and three phenyl rings. Structure 3 is a multivalomer with a central triazine ring and three phenyl rings, each with a bromine atom.

(a) Bu_3SnN_3 , xylene, 24 hr reflux (b) NaOH , THF

For precedent see Carini, D. J., J. Med. Chem., 1991, 34, 2525-2547

FIG. 46

FIG. 47

FIG. 49

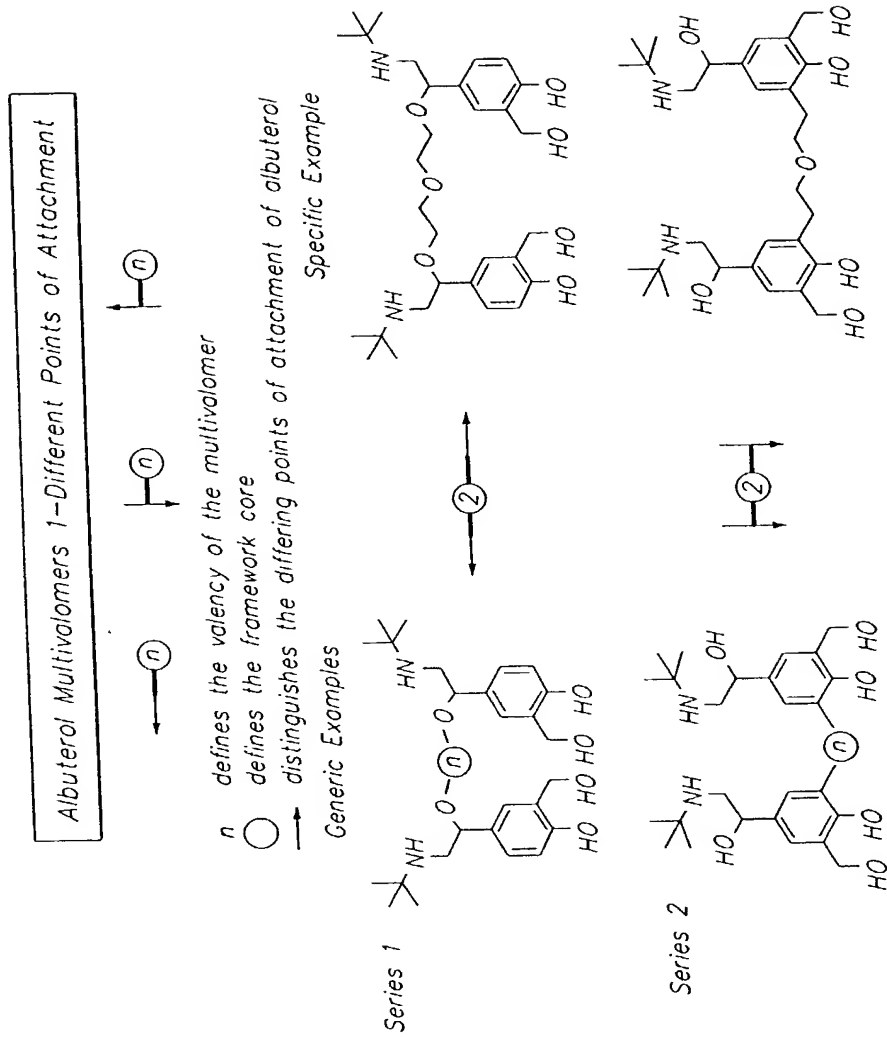


FIG. 50A

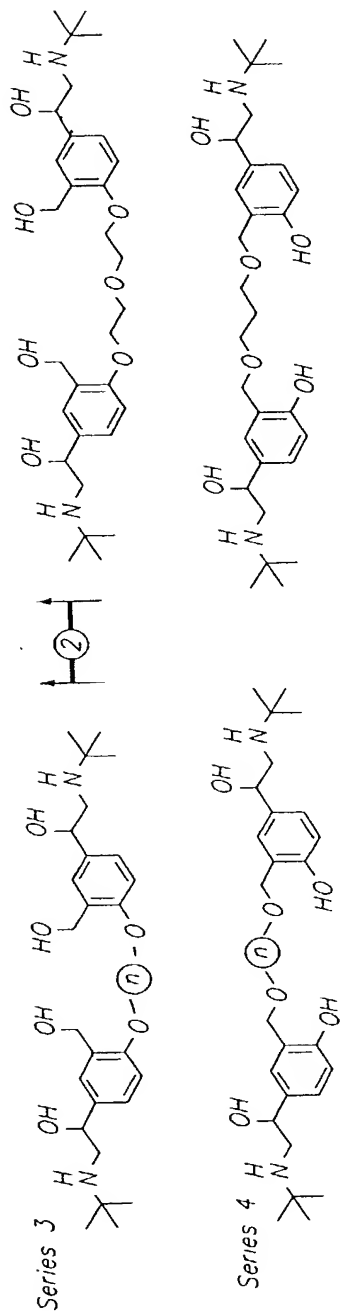


FIG. 50B

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Albuterol Multivalomers 2-Alternative Framework Cores

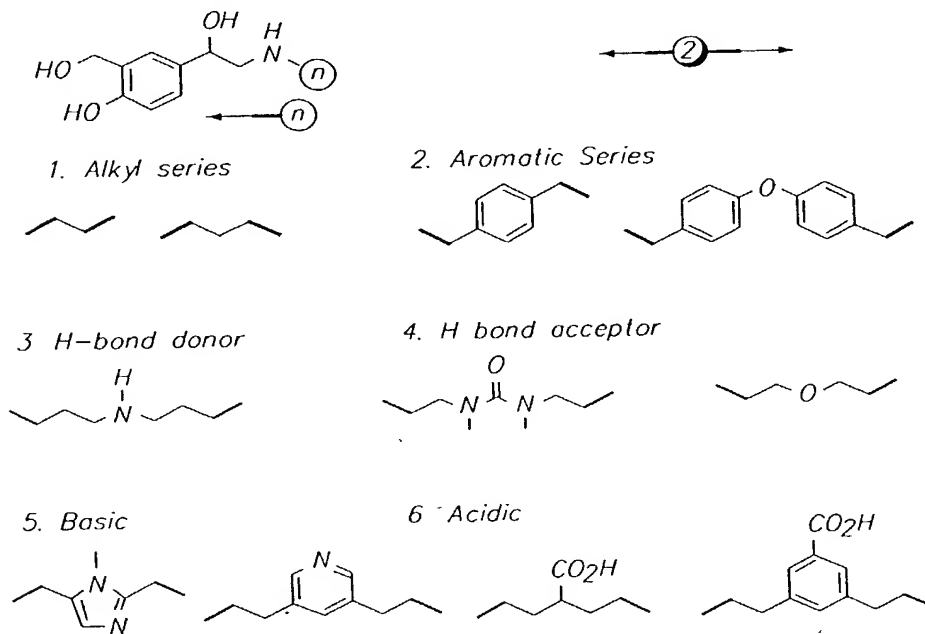


FIG. 51

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Albuterol Multivalomers 4-Relative Pharmacophore Orientation

Pharmacophore Orientation

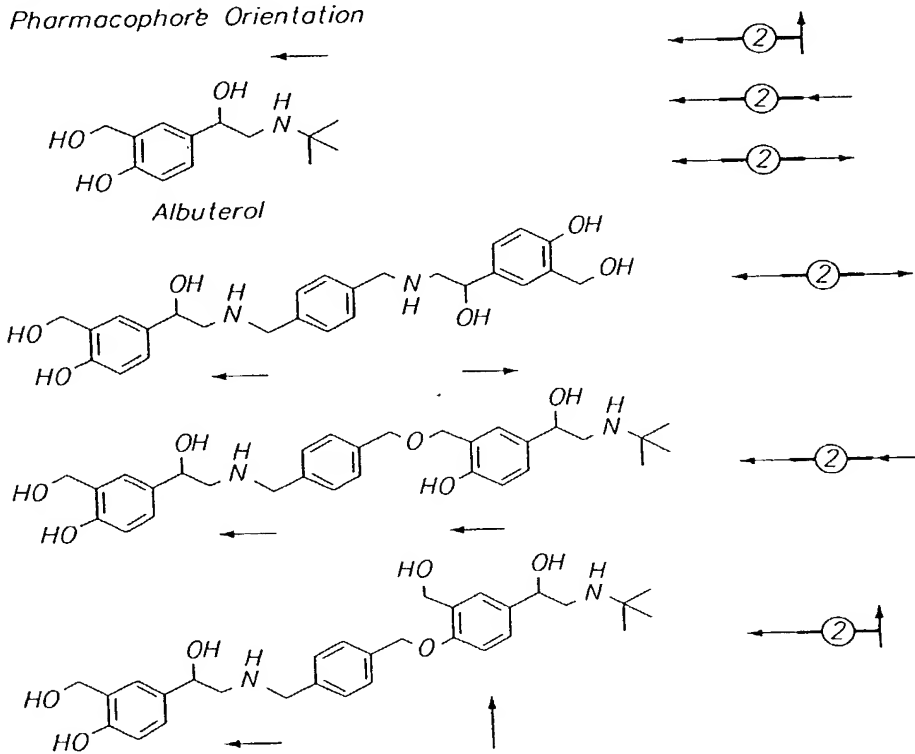


FIG. 53

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Albuterol Multivalomers 5-Mixed β_2 Adrenergic Heterovalomers

Heterovalomers

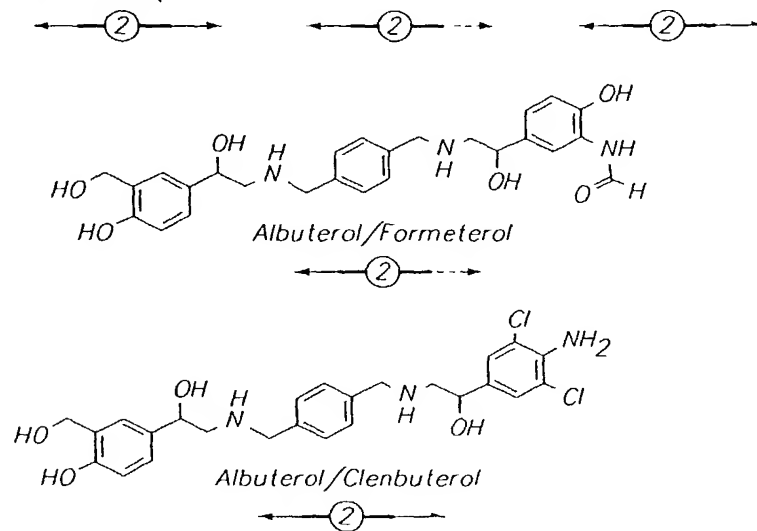
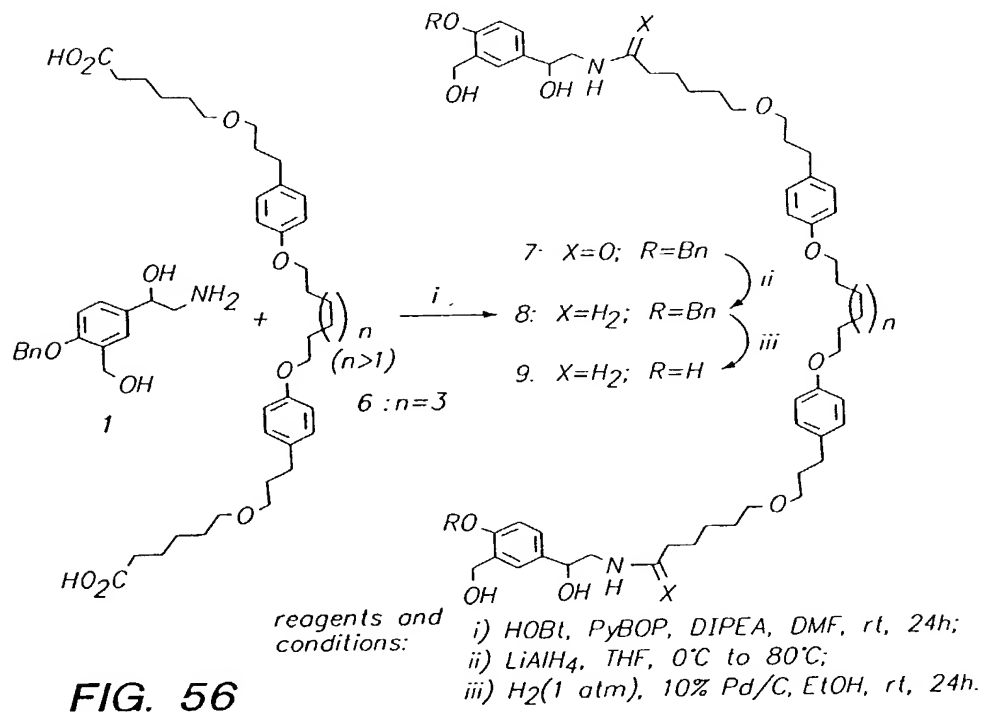
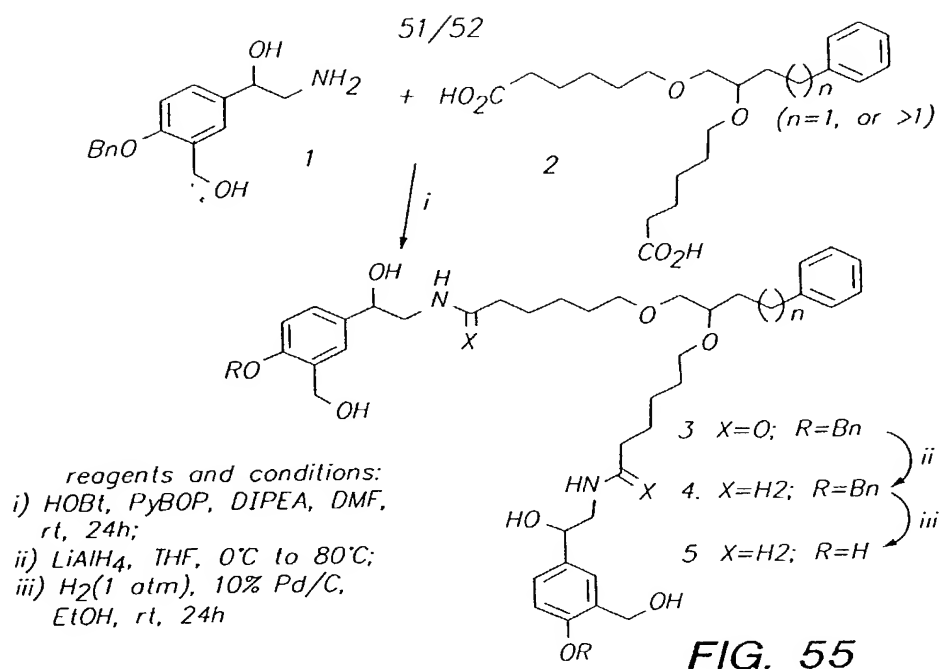
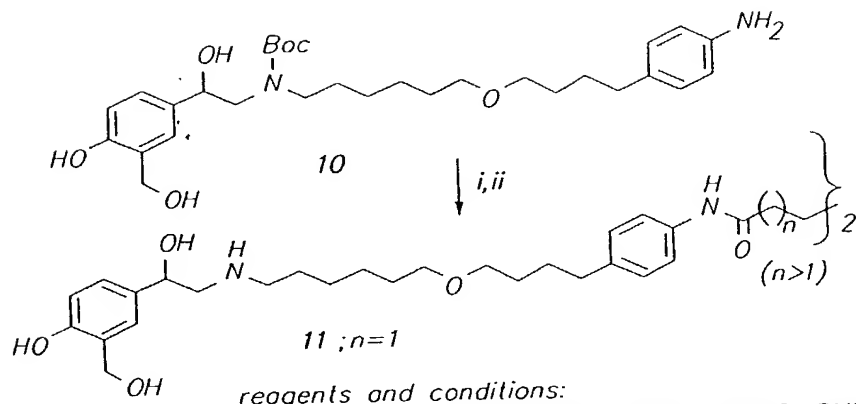


FIG. 54

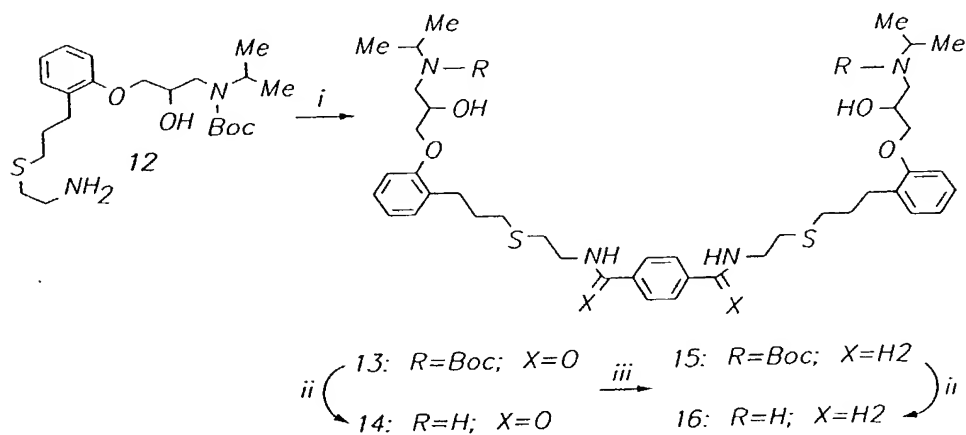


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reagents and conditions:
 i) 1,6-hexanedioic acid, DIPEA, HOBT, PyBOP, DMF, rt.
 ii) TFA/CH₂Cl₂, 0°C.

FIG. 57



reagents and conditions:
 i) terphthalic acid, DIPEA,
 HOBT, PyBOP, DMF, rt;
 ii) TFA/CH₂Cl₂, 0°C;
 iii) LiAlH₄, THF, 80°C;

FIG. 58